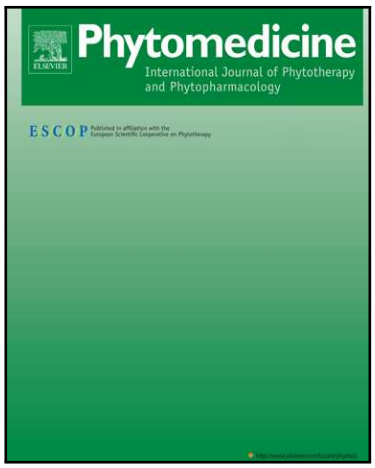

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Liver transplantation and the use of KAVA: Case report

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ABSTRACT

Background: Self-medication and the belief that herbal products are free of health risks are common in Brazil. The kava (Piper methysticum), known for its anxiolytic action, has a widespread popular use. Hepatotoxicity of kava is reported, including cases of liver transplantation and death. The kava had its use prohibited or restricted in countries like Germany, France, among others. Toxicity may be related to overdosage; however, factors such as botanical characteristics of the plant, the harvesting, storage, and production process may be associated with the development of hepatotoxic substances, such as triggering idiosyncratic reactions. *Hypothesis:* In this case, there is a suspicion that the toxicide is intrinsic to the drug; however, the possibility of adulterants and contaminants must be ruled out.
Study design: This study reports the case of a patient who, after using the herbal kava for 52 days, evolved into acute liver failure and liver transplantation.
Methods: The data were collected directly with the patient and compared with their clinical records. Causality was determined through the RUCAM algorithm. In addition, a phytochemical analysis of the drug used was performed.
Results: According to the patient's report, there is no evidence of overdosage. Results from RUCAM algorithm infer causality between liver damage and the use of kava. The analysis chemical constituents did not find any possible contaminants and major changes in the active compounds. Seven months after transplantation, the patient is well and continues to be followed up by a medical team.
Conclusion: Our investigation indicates that there was kava-induced hepatotoxicity at standard dosages. In Brazil, self-medication by herbal medicines is frequent and many patients and health professionals do not know the risks associated with their use. Diagnosing and notifying cases in which plants and herbal medicine induce liver damage is of paramount importance to increase the knowledge about DILI and to prevent or treat similar cases quickly.

Keywords: Chemical and Drug Induced Liver Injury; Kava; Liver Transplantation; Liver Failure, Acute; Phytotherapy

Abbreviations

DILI – Drug-Induced Liver Injury, HPLC/ESI-MS/MS – high-performance liquid chromatography coupled with accurate quadrupole-time of flight mass, pectrometer/electrospray ionization, QD – Once a day, RUCAM – Russel Uclaf Causality Assessment Method, WHO – World Health Organization

Introduction

The kava extract is an herbal medicine widely used worldwide for anxiety treatments. In 2001, it was among the top-selling herbs in the United States (Blumenthal, 2002). In 2003, Cochrane's review concluded that kava extract (regardless of the type of extract, only monotherapy studies were included) was effective for the treatment of anxiety and safe to use for up to 24 weeks (Pittler and Ernst, 2003). However, kava pyrones, the active compounds responsible for the pharmacological effect, are associated with hepatotoxicity and even had their use banned or restricted in the European and American markets (CDC, 2002).The traditional

kava drink produced from aqueous extract of the roots of *Piper methysticum*, widely utilized by South Pacific islanders, was considered to be safe (Stevinson et al., 2002).

In the Brazilian regulatory aspect, herbal medicines follow a simplified registration system. For kava, the following specifications must be met: extract obtained from the rhizome of the herb, and a daily allowable dose of 60 to 120 mg of kavapyrones. Its use is approved for anxiety, agitation, insomnia, and nervous tension. After the Food and Drug Administration alert, the Brazilian Health Regulatory Agency restricted the kava use to dispensing under medical prescription and a maximum period of use for up to two months (ANVISA, 2002).

About kava hepatotoxicity, the WHO reports 93 case analyses, but most of them lack good clinical documentation to determine the causality; moreover, they did not use a specific method to define hepatotoxicity (Coulter et al., 2007). In 2010, a study reporting 31 cases found it to be highly probable or probable in only 5 cases (Teschke, 2010).

The kava toxicity mechanism is still unclear. Poor-metabolizer phenotypes of CYP2D6 hypotheses had more toxicity events (Russmann et al., 2003). Kavalactones are related to some processes such as inhibition of CYP enzymes, as well as cyclooxygenase (COX-1, COX-2) or depletion of hepatic glutathione (Pantano et al., 2016). There is evidence the DILI's susceptibility could be genetically determined (Urban et al., 2014). Besides, toxicity may be related to intrinsic hepatotoxic metabolites or contaminants, from harvesting to storage process (Teschke et al., 2013).

The major difficulty of associating kava with hepatotoxicity may be related to the nonspecific symptoms of this injury. In clinical practice, the RUCAM algorithm is the best method to assess the causality of drug-induced liver disease and, when applied, it increases the likelihood of hepatotoxicity being actually related to the drug and not to other events (Danan and Teschke, 2015).

This is a case report of an acute liver failure after 52-day use of kava and clinical progression to liver transplantation. We performed a chemical analysis of this herbal medicine, considering possible contaminants, adulterants, and other agents for liver toxicity.

Case Report

Female, 45 years old, admitted to a small hospital on 09/05/2016 with symptoms of nausea and jaundice since 09/03/2016. Computed tomography of abdomen within normality. Total bilirubin: 12.40mg/dl; direct bilirubin: 10.40mg/dl; Alanine methyltransferase: 2459 U/L; international normalized ratio: 1.76 (Graph 1). In anamnesis, the patient disclaims alcoholism and smoking. Previous use of continuous drugs: omeprazole 20mg QD for 4 years and bromazepam 3mg QD for 2 years. Patient reports stop using bromazepam and self-medicating with herbal kava medicine 100mg QD at night. The symptoms started 52 days after the onset of kava use. On 09/05/2016, after hospital admission, the kava medication was suspended.

Infectious diseases, such as hepatitis A, B, C, cytomegalovirus, Epstein bar virus, leptospirosis, and herpes, were excluded.

In 09/15/2016, the patient was transferred to a medium-complexity center, where tests for autoimmune hepatitis and toxoplasmosis were performed, both with negative results. She was diagnosed with severe acute hepatitis and transferred (09/17/2016) to a Transplantation Center in Porto Alegre, Rio Grande do Sul, Brazil. Upon admission to the Transplantation Center, the patient did not present hepatic encephalopathy. In 09/18/2016, she developed acute kidney failure, requiring renal replacement therapy until 09/20/2016. From 09/22/2016 she evolved into hepatic encephalopathy, configuring the syndromic diagnosis of acute liver failure, with the King's College criteria indicating the need for liver transplantation (age over 40 years, total bilirubin greater than 17.5 mg/dl, hepatotoxic etiology, and evolution from jaundice to encephalopathy > 7 days) (O'Grady, 2014), being listed as urgency on 9/23/2016. While awaiting ABO-compatible organ offer, single-pass albumin dialysis (SPAD) was associated with continuous venous hemofiltration as of 09/24/2016, for concomitant artificial liver and renal support (Tsipotis et al., 2015).

Liver transplantation performed on 09/27/2016. The explanted organ had submassive necrosis. Patient presented postoperative hemorrhagic shock, requiring high-doses vasopressors and massive transfusion of hemoderivatives. A new surgical intervention was done in 09/30/2016 by abdominal compartment syndrome, with removal of clots from the cavity. After, the patient presented progressive clinical improvement and was extubated on 10/10/2016, dialysis support was suspended on 10/12/2016, and she was discharged from the ICU on 10/15/2016. She also received empirical antibiotic therapy for post-operative nosocomial bacterial infections, in addition to ganciclovir for cytomegalovirus infection. She was sent home on 11/28/2016 and has been evolving favorably ever since. After seven months of post-transplantation, the patient is well and continues to be followed up by a multi professional care team.

Rucam

The RUCAM algorithm was applied to determine causality, according to the medical records and interviews performed with the patient. RUCAM score was 8 (Fig.1), as kava was probably associated with liver hepatotoxicity.

Temporal relations between the onset of kava use and the onset of symptoms, as well as the suspension and decline of liver markers, was of great importance to reinforce the degree of causality of the injury. Moreover, the patient did not present associated risk factors such as age > 55 years and use of alcohol > 2 doses a day. Varicella was not investigated.

RUCAM algorithm information was collected later. Thus, for the elucidation of DILI cases, some information about previous pharmacotherapy, clinical tests, and diseases is required. The RUCAM algorithm can be applied later, but a memory bias could be present.

Regulatory agency notified

In Brazil, adverse drug reactions should be reported to the health regulatory body. The national health surveillance agency is the regulatory department that receives and monitors these reports. Since 2009, there is an online system for reporting adverse drug reactions, where patients, health professionals, and companies can report them. This case was reported to the regulatory department, the pharmacy, as well as to the kava producer. In addition, the quality control reports of the raw material were requested from the drug producer.

Kava analysis

The quality control reports indicated extraction with methanol, and all the chemical and microbiological requirements were met. The capsules used by the patient were submitted to constituents and contaminants investigation.

Chemo-profiling was performed by HPLC/ESI-MS/MS. The drug used by the patient was compared to a sample purchased at the same pharmacy a few months later. In this study, the drug purchased by the researchers was considered the control. Both medicines were 100-mg kava capsules.

For the possible contaminants, Aflatoxins (AfB1, AfB2, AfG1, AfG2 e AfM1) and Ochratoxin A were researched by HPLC/ESI-MS/MS, with the Multiple Reaction Monitoring method.

The results showed that all Kavalactones, Flavocaine B, Pipermetistina, and other specifications were within the standards. Similarly, the research for Aflatoxins and Ochratoxin A was negative. Graph 2 shows that there was some reduction in the concentration of constituents in the patient sample, however, this can be attributed to the natural degradation of the drug. Besides, the environmental conditions in which the plant developed could also contribute to the constituents variation (Graphs 2 and 3). We reject the hypothesis that there are high concentrations of the kava active compounds. However, we cannot accurately state that the capsule had 100 mg of kava since the control used was not a standard.

Discussion

This is the first detailed case report of liver transplantation associated with kava in Brazil. In a retrospective study with data from the national registry based on adverse events reports, 2 kava deaths were reported, although without mentioning the causality assessment (Balbino and Dias, 2010).

In other countries, between 1998 and 2001, seven cases were published, with 5 cases of liver transplantation and one death. These episodes led to the kava ban in the German market and, consequently, in other countries. Later, between 1990 and 2002, 29 unpublished cases were identified and notified to the regulatory agency in Germany, as well as 8 liver transplantations and 3 deaths. Kava-induced hepatotoxicity was calculated as 0.26 cases/1 million daily doses (Stickel et al., 2003). However, the German cases were re-analyzed and it was assumed that many of them were poorly assessed as to causality and there could be interferers that would remove suspicion of DILI. Of the 19 cases, only 1 poresented very likely association and one with probable; however, many cases lacked information (Teschke et al., 2003).

Subsequently, 26 cases from German and Swiss regulatory agencies were re-analyzed, including the missing information recovered and RUCAM application, and a probable causal relationship to kava was assessed in a single case in which it was being used according to the recommendations (Teschke et al., 2008).

A worldwide security study alerted about the concern related to kava products and hepatotoxicity. Also, in the organic extract, other chemicals could be associated with hepatotoxicity. Some risk factors for hepatic reactions seem to be the use of organic extracts, alcoholism, liver disease, genetic polymorphisms, and overdosage. Furthermore, co-medication with other potentially hepatotoxic drugs and interacting drugs, particularly other anxiolytics, antipsychotics, and anti-thrombotics, might lead to harm (Organization, 2007).

Thus, it was also proposed that a possible liver injury could be associated with hepatotoxic contaminants or metabolites from the plant's extraction process or intrinsic form (Teschke et al., 2011a). Yet, overall, a careful cultivation; the selection of the correct raw materials; extraction in aqueous solvent; use of a maximum of 250 mg of kavalactones per day, avoiding prolonged use; systematic and rigorous research on the subject, and a strict quality control system are important points that can prevent toxicity by kava (Teschke et al., 2011b).

In this rare case, we excluded the intrisic and extrinsic toxicity of kava after performing chemical analyzes of the drug used and possible contaminants. As limitations of this study, we emphasize that the analyzes were performed without a standard for kava and that it was impossible to analyzes the genetic susceptibility of this patient.

Conclusions

Kava-induced hepatoxicity and transplantation are rare, but this DILI hypotesis is probable according to the RUCAM algorithm and the chemicals and contaminants analyses. The medical record, the interview with the patient, and collaborations of health professionals were crucial to elucidated such association.

This case is unique, as it is the first case report of liver transplantation due to kava in Brazil, although it is obviously not the first – we verified that the lack of data erroneously

suggests the inexistence of similar cases. This suggests the need for stimulating the notification, correct evaluation, and publication of existing cases.

In a global context, there is no study yet that investigated the sample used by the patient to exclude contaminants and intrinsic toxicity of the substance. This case was thoroughly investigated and a probable causality was established between kava and liver injury. The patient progressed favorably, since such was correctly identified and quickly managed in all stages, from the initial diagnosis to the post-transplant care. Thus, this case served as a model from the first care until the later investigation of the causality of a DILI patient. Nonetheless, it should be emphasized that the algorithm used does not replace the clinical skills and should be associated with the opinion of an expert to handle the case.

Conflict of interest

There is no conflict of interest.

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Items for Hepatocellular Injury	Score	Result
1. Time to onset from the beginning of the drug/herb		
5–90 days (rechallenge: 1–15 days)	+2	**+2**
<5 or >90 days (rechallenge: >15 days)	+1	
Alternative: Time to onset from cessation of the drug/herb		
<15 days (except for slowly metabolized chemicals: >15 days)	+1	
2. Course of ALT after cessation of the drug/herb Percentage difference between ALT peak and N		
Decrease >50% within 8 days	+3	**+3**
Decrease >50% within 30 days	+2	
No information or continued drug use	0	
Decrease > 50% after the 30th day	0	
Decrease < 50% after the 30th day or recurrent increase	-2	
3. Risk factors		
Alcohol use (current drinks/day: >2 for women, >3 for men)	+1	
Alcohol use (current drinks/day: <2 for women, <3 for men)	0	**0**
Age > 55 years	+1	
Age < 55 years	0	**0**
4. Concomitant drug(s)/herb(s)		
None or no information	0	
Concomitant drug/herb with incompatible time to onset	0	**0**
Concomitant drug/herb with compatible or suggestive time to onset	-1	
Concomitant drug/herb known as hepatotoxin and with compatible or suggestive time to onset delete marking right side above	-2	
Concomitant drug/herb with evidence for its role in this case (positive rechallenge or validated test)	-3	
5. Search for alternative causes	Tick if Negative	Tick if not done
Group I (7 causes)		
HAV: Anti-HAV-IgM	″	″
Hepatobiliary sonography / colour Doppler	″	″
HCV: Anti-HCV, HCV-RNA	″	″
HEV: Anti-HEV-IgM, anti-HEV-IgG, HEV-RNA	″	″
Hepatobiliary sonography/colour Doppler sonography of liver vessels/ endosonography/CT/MRC	″	″
Alcoholism (ASŦ/ALT 2)	″	″
Acute recent hypotension history (particularly if underlying heart disease)	″	″
Group II (5 causes)		
Complications of underlying disease(s) such as sepsis, metastatic malignancy, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cholangitis or sclerosing cholangitis, genetic liver diseases	″	″
Infection suggested by PCR and titer change for		
CMV (anti-CMV-IgM, anti-CMV-IgG)	″	″
EBV (anti-EBV-IgM, anti-EBV-IgG)	″	″
HSV (anti-HSV-IgM, anti-HSV-IgG)	″	″
VZV (anti-VZV-IgM, anti-VZV-IgG)	″	″
Evaluation of groups I and II		
All causes-groups I and II—reasonably ruled out	+2	
The 7 causes of group I ruled out	+1	**+1**
6 or 5 causes of group I ruled out	0	
Less than 5 causes of group I ruled out	-2	
Alternative cause highly probable	-3	
6. Previous hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	+2	**+2**
Reaction published but unlabelled	+1	
Reaction unknown	0	
7. Response to unintentional reexposure		
Doubling of ALT with the drug/herb alone, provided ALT below 5N before reexposure	+3	
Doubling of ALT with the drug(s)/herb(s) already given at the time of first reaction	+1	
Increase of ALT but less than N in the same conditions as for the first administration	-2	
Other situations	0	**0**
Total score for the case		**+8**

Figure 1. The patient's score in the RUCAM algorithm was compatible with probable causality with score 8.

Graphical abstract